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| EXAMINER |
|---|
| BUNNER, BRIDGET E |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 11 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/731,255 | HABENER ET AL. | |
| | Examiner | Art Unit | |
| | Bridget E. Bunner | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-127* is/are pending in the application.

4a) Of the above claim(s) *1-24,36-66 and 80-127* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-35 and 67-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-127* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election of Group III, claims 25-35 and 67-69 in Paper No. 10 (23 September 2002) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-24, 36-66, and 80-127 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10 (23 September 2002).

Claims 25-35 and 67-79 are under consideration in the instant application.

### *Sequence Compliance*

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. **Specifically, the specification discloses primer sequences at pages 22-24 and 50 that are not accompanied by the required reference to the relevant sequence identifiers. Furthermore, the sequences disclosed in Figure 2 and Figure 7 are not accompanied by the required reference to the relevant sequence identifiers.** Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

### *Specification*

2. The disclosure is objected to because of the following informalities:

2a. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

2b. In the specification, the last paragraph at the bottom of page 3 (lines 20-23) is the same paragraph at the top of page 4 (lines 1-4). Please delete one of these paragraphs.

2c. The Brief Description of Drawings for Figure 4 does not refer to Figures 4A-4B.

2d. The Brief Description of Drawings for Figure 7 does not refer to Figures 7A-7C.

2e. The Brief Description of Drawings for Figure 8 does not refer to Figures 8A-8E.

2f. The Brief Description of Drawings for Figure 9 does not refer to Figures 9A-9C.

2g. The Brief Description of Drawings for Figure 10 does not refer to Figures 10A-10D.

2h. The Brief Description of Drawings for Figure 11 does not refer to Figures 11A-11C.

2i. The Brief Description of Drawings for Figure 15 does not refer to Figures 15A-15C.

2j. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD OF TREATING DIABETES MELLITUS BY ADMINISTERING A PSEUDO-ISLET LIKE AGGREGATE DIFFERENTIATED FROM A NESTIN-POSITIVE PANCREATIC STEM CELL".

Appropriate correction is required.

***Claim Objections***

3. Claims 25-26 and 68-69 are objected to because of the following informalities:

Claims 25-26 and 68-69 should put parentheses around reference to step a (i.e., "step (a)"). See claim 25(d), line 2 and claims 26 and 68-69, line 2.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 25-35 and 67-79 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, claims 25-35 and 67-69 are directed to a method of treating a patient with diabetes mellitus or a method of transplanting into a mammal, comprising the steps of: (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet, (b) expanding the stem cell to produce a progenitor cell, (c) differentiating the progenitor cell in culture to form pseudo-islet like aggregates, and (d) transferring the pseudo-islet like aggregates into the patient. The claims also recite that the donor is a patient/mammal is a human and the donor is a non-human mammal. The claims recite that the patient/mammal is not treated with an immunosuppressive agent prior to step (b). The claims also recite that the step of expanding is performed in the presence of an agent and the step of transferring is performed via endoscopic retrograde injection.

The specification of the instant application teaches that one embodiment of the invention provides an alternative to transplantation of stem cells or progenitor cells by causing them to form pseudo-islet like aggregates that can be transplanted into a patient with insufficient islet cell

mass to maintain physiological control without hormone therapy (pg 29, lines 18-21). The specification also discloses that after a diabetic patient undergoes pancreatic biopsy, islets are isolated from the biopsy tissue and prepared for culture *ex vivo* preferably within 24 hours. The specification continues to teach that stem cells can be proliferated and isolated within 2-3 weeks and transplanted back into the patient (pg 33, lines 20-27). Although the specification of the instant application teaches isolating a nestin-positive pancreatic stem cell from a pancreatic islet, expanding the stem cell to produce a progenitor cell, and differentiating the progenitor cell in culture to form pseudo-islet like aggregates (pg 42-44; 51-55), the specification does not teach transferring the pseudo-islet like aggregates into any patient, especially to treat diabetes mellitus. The disclosure in the instant application is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. For example, the prophetic example does not teach the skilled artisan the optimal dosage, duration, and mode of administration of the pseudo-islet like aggregates. The skilled artisan must resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of the pseudo-islet like aggregates. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed." Furthermore, the claimed composition may not necessarily treat a patient with diabetes mellitus. The specification does not teach that the transplanted pseudo-islet like aggregates act like healthy islet cells. For example, there are no methods or working examples that indicate the pseudo-islet like aggregates would have any effect on blood glucose or insulin, which is required for diabetes treatment. The state of the art is also such that

patients may suffer one of two types of graft or transplant rejections, host-versus-graft rejection or graft-versus-host rejection (GvHR). In host-versus-graft rejection, the patient's immune cells have an immune response to the graft's antigens while in GvHR, the graft rejects the patient's tissues. Since claim 25 recites that the patient does not serve as the donor for the nestin-positive pancreatic stem cells, the skilled artisan cannot predict that the differentiated pseudo-islet like aggregates can be successfully immunologically transplanted into the recipient patient. Furthermore, the specification of the instant application does not disclose the identity of the nestin-positive pancreatic stem cell donor. For example, the cells could be from another human, a pig, monkey, rat, etc. and therefore possibly cause host-versus-graft rejection or GvHR in the recipient patient.

Additionally, relevant literature reports that cells that express nestin are undoubtedly present in the developing and adult pancreas, but correspond to mesenchymal cells that initially surround pancreatic buds and later become dispersed among the branching epithelial cells (Edlund, H. Nature Rev Genet 3: 524-532, 2002; pg 530, bottom of col 2). Edlund also teaches that the epithelium of the entire gastrointestinal tract is surrounded by mesechyme that consist of nestin-positive cells. Edlund states that throughout the development and in the adult, markers of pancreatic progenitors and differentiated pancreatic cell types are expressed in epithelial cells that do not express nestin. Edlund concludes that since nestin is not expressed in pancreatic epithelial cells at any stage of development, nestin is an inappropriate marker for pancreatic cell types (pg 531, top of col 1). In contrast the claims of the instant application, Edlund indicates that above observations, in combination with the similarities between pancreatic endocrine cells

and neurons, call for caution and stringency when analyzing marker gene expression in attempts to generate β-cells from stem cells (pg 531, first full ¶).

Due to the large quantity of experimentation necessary to transfer pseudo-islet like aggregates into a patient and treat diabetes, to determine the activity of the pseudo-islet like aggregated once administered, and to determine the optimal dosage, duration, and mode of administration of the pseudo-islet like aggregates, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the art (see discussion above), and the unpredictability of the activity and immunologic effects of the pseudo-islet like aggregates once administered to the patient, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

***35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 25-35, 72 and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Regarding claims 28, 35, 72, and 79, the acronyms "EGF", "bFGF-2", "KGF", "HGF/SF", "GLP-1", "IDX-1", "TGF-β", "FK-506", and "GAD65" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

7. Claims 25-35 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating that transferring the pseudo-islet like aggregates into the patient treats diabetes mellitus.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 25, 28-30, and 35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13 and 15-18 of copending Application No. 09/731,261 and claims 19 and 24-27 of copending Application No. 09/963,875. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the '261 application, the '875 application, and the instant application recite isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor, expanding the stem cell to produce a progenitor cell, differentiating the progenitor cell, differentiating the progenitor cell in culture to form pseudo-islet like aggregates, transferring the pseudo-islet like aggregates into the patient. The claims in all the applications also recite that the step of expanding is performed in the presence of an agent, the step of transferring is performed via endoscopic retrograde injection, and the method additionally comprises of treating the patient

with an immunosuppressive agent, wherein the immunosuppressive agent is selected from one of a group of agents. The difference between the claims of the '261 application, the '875 application and the instant application is that the method of the instant application specifically recites that the patient does not serve as the donor for the stem cells. Claim 13 and 15-18 of the'261 application and claims 19 and 24-27 of the '875 applications are silent as to the donor of the stem cells. Therefore, the claims of the instant application are not patentably distinct over the copending claims in Application Nos. 09/731,261 and 09/963,875.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 67-68, 72-74, and 79 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-18 of copending Application No. 09/731,261 and claims 19 and 23-27 of copending Application No. 09/963,875. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the '261 application, the '875 application, and the instant application recite isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor, expanding the stem cell to produce a progenitor cell, differentiating the progenitor cell, differentiating the progenitor cell in culture to form pseudo-islet like aggregates, transferring the pseudo-islet like aggregates into a subject. The claims in all the applications also recite that the subject serves as the donor for the stem cells, the step of expanding is performed in the presence of an agent, the step of transferring is performed via endoscopic retrograde injection, and the method additionally comprises of treating the subject with an immunosuppressive agent, wherein

the immunosuppressive agent is selected from one of a group of agents. The difference between the claims of the '261 application, the '875 application and the instant application is that the method of the instant application recites transferring the pseudo-islet like aggregates into a mammal (rather than a patient, as recited in the copending applications). Additionally, the administration of the same recited cells and agents to a subject will elicit the same response in the body, regardless of the phrasing of the preamble. Therefore, the claims of the instant application are not patentably distinct over the copending claims in Application Nos. 09/731,261 and 09/963,875.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Conclusion***

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Lumelsky et al. Science 292: 1389-1394, 2001.

Efrat, S. Diabetes 50(Suppl): S189-S190, 2001.

Yamaoka, T. Biochem Biophys Res Comm 296: 1039-1043, 2002.

Zulewski et al. Diabetes 50: 521-533, 2001.

Bonner-Weir S et al. J Pathol. 197(4):519-26, 2002.

Peck et al. U.S. Patent No. 6,001,647

Brothers, A. U.S. Patent No. 6,372,493

Fung et al. U.S. Patent No. 6,326,201

Roberts et al. U.S. Patent No. 6,436,704

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elyabeth C. Kemmerer

BEB
Art Unit 1647
November 22, 2002